Case report

Brain metastases in patients with low-grade endometrial carcinoma

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A B S T R A C T

Objective: To report characteristics of patients with low-grade endometrioid endometrial carcinoma (EC) who develop brain metastases.
Methods: We retrospectively identified all patients treated at our institution for FIGO grades 1/2 EC from 1/2000–12/2016, who developed brain metastases. Electronic medical records were reviewed, data abstracted. Overall survival (OS) was determined from time of brain metastases to death or last follow-up. Appropriate statistical tests were used.
Results: Of 3052 patients, 23 (9, grade 1; 14, grade 2) developed brain metastases (incidence = 0.75%). Presentation at initial diagnosis: median age = 61.3 years (range, 41–81); median BMI = 29.8 kg/m^2 (range, 20.3–42.6 kg/m^2); distribution by stage: I, 15/23 (65%); II, 2/23 (8.7%); III, 3/23 (13.0%); IV, 3 (13.0%). None showed clinical evidence of brain metastases at presentation. Median time to diagnosis of brain metastases = 29.7 months (range, 6–145); median age = 64.6 years (range, 47.5–86.5). Brain metastases were the first, isolated site of recurrence in 2/23 (9%). All presented with neurological symptoms. Six (26%) had solitary brain lesions. Seventeen (74%) received treatment; 6 (28%), supportive care only. Median OS for patients receiving any treatment = 5.8 months (95% CI, 1.6–10.0), versus 2.4 months (95% CI, 1.5–3.3; *p* = .04) for best supportive care.
Conclusion: Brain metastases in low-grade EC is rare, prognosis generally poor. Compared to supportive care only, any treatment results in more favorable outcomes.

1. Background

Endometrial cancer (EC) is the most common malignancy of the female genital tract, affecting approximately 320,000 women worldwide. Many of these cancers (> 90%) have endometrioid histology (Torre et al., 2015). The incidence of EC is growing, including in premenopausal women, and is partly driven by increasing rates of obesity (Onstad et al., 2016; Lortet-Tieulent et al., 2018). Most patients have early-stage, low-grade disease (Jamison et al., 2013). Following primary therapy, 5-year overall survival (OS) for Stage 1 disease is > 95% (NIH National Cancer Institute Surveillance, n.d.). Disease recurs through lymphatic and local spread in 10–30% of patients, and is frequently confined to the abdomen and pelvis (Elliott et al., 2004).

Brain metastases via hematogenous spread is not uncommon in lung, breast, renal and colorectal cancers (Nussbaum et al., 1996). However, brain involvement in EC is rare, with a total of only 115 documented cases in the literature (Piura & Piura, 2012). Previous reports cite an incidence of < 1%, the majority arising from high-grade histologies (Piura & Piura, 2012; Cormio et al., 1996; Uccella et al., 2016). The objective of this study was to report its prevalence, as well as the characteristics of patients diagnosed with low-grade (FIGO grades 1 and 2) EC, treated at a single cancer specialty center, who subsequently developed brain metastases.

2. Methods

This study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSKCC). We identified 23 women with initial diagnosis of low-grade (FIGO grades 1 and 2) EC, treated at MSKCC between January 2000 and December 2016, who developed brain metastases. Their medical records were reviewed in detail for demographic, tumor and treatment data, and the following information was abstracted: age at diagnosis of EC, stage and histology of the primary tumor, lymphovascular space invasion (LVSI), primary

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Table 1
Characteristics of patients with grade 1–2 endometrial cancer who developed brain metastases (n = 23).

Characteristics	N
Median age at diagnosis (yrs)	
Median (range)	61 (41–81)
FIGO[a] Grade at Diagnosis	
1	9 (39%)
2	14 (61%)
FIGO (2009) Stage at diagnosis	
I	15 (65%)
II	2 (9%)
III	3 (13%)
IV	3 (13%)
Median BMI[b] at diagnosis (range)	29.8 (20.3–42.6)
Overweight (BMI 26–29.9 kg/m^2)	19 (83%)
Obese (BMI > 30 kg/m^2)	11 (48%)
Treatment at initial diagnosis	
Surgery	7
Surgery + chemotherapy	1
Surgery + chemotherapy + radiation	2
Surgery + radiation	10
Chemotherapy	2
Chemotherapy + radiation	1
Pathologic characteristics	
Lymphovascular space invasion (n = 20)	8 (40%)
Endocervical invasion (n = 20)	3 (15%)
Pelvic washings positive (n = 16)	1 (6%)
Median time to brain metastases (months)	
Median (range)	29.7 (95% CI, 16.7–42.7)
Median age at recurrence (years)	
Median (range)	66.5 (47.5–86.5)
Clinical Manifestations of brain metastases	
Altered mental status	6 (26%)
Headache, visual changes	7 (30%)
Weakness, unsteady gait	9 (39%)
Seizure	1 (4%)
Site of brain lesion	
Right	5 (22%)
Left	4 (17%)
Bilateral	14 (61%)
Cerebellum	6 (26%)
Number of brain lesions	
Single	6 (26%)
Multiple	17 (74%)
Management of brain metastases	
Surgery + chemotherapy	2 (9%)
Surgery + chemotherapy + radiation	4 (18%)
Surgery + radiation	3 (13%)
Chemotherapy + radiation	1 (4%)
Radiation	7 (30%)
Supportive care	6 (26%)
Median overall survival	
From initial diagnosis of EC (95% CI)	36.1 (95% CI, 18.7–53.5)
From diagnosis of brain metastases (95% CI)	5.1 (95% CI, 2.2–8.1)
Deceased	20 (87%)

[a] FIGO, International Federation of Gynecology and Obstetrics.
[b] BMI, Body mass index.

and adjuvant treatment, age at diagnosis of brain metastases, location and number of brain metastases, interval between initial diagnosis of the primary tumor and onset of brain metastases, and interval between completion of primary treatment and development of brain metastases. Staging was based on the 2009 International Federation of Gynecologists and Obstetricians (FIGO) classification system. Each brain recurrence was categorized as being either concomitant with recurrences in other organ sites, or as an isolated recurrence. Patients were censored at date of death or date of last follow-up. Overall survival (OS) was determined from the date of diagnosis of brain metastases to the time of documented disease progression or death. Survival was estimated using the Kaplan–Meier method, and estimates were compared with the log-rank test. All statistical tests were performed using SPSS® Statistics 25.0 software.

3. Results

Among 3052 patients with low-grade EC, 23 patients (9, FIGO grade 1; 14, FIGO grade 2) developed brain metastases (an incidence of 0.75%). Detailed patient characteristics are presented in Table 1. The median age at initial diagnosis was 61.3 years (range, 41–81 years). Distribution by stage was as follows: Stage I, 15/23 (65%); Stage II, 2 (8.7%); Stage III, 3 (13.0%); Stage IV, 3 (13.0%). None showed clinical evidence of brain metastases at initial presentation. Patients with Stage IV disease at diagnosis (n = 3) did not undergo initial comprehensive surgical staging; 1 of these patients had bone metastases, 1 had a positive axillary node, and 1 had a positive supraclavicular node. The remaining 20 patients underwent comprehensive staging, including total hysterectomy and bilateral salpingo-oophorectomy. Three patients had an omentectomy, and peritoneal washings were collected in 16 patients. A pelvic lymph node dissection/sampling was performed in 16 patients, with a median of 18 lymph nodes removed (range, 0–33). Eight of 20 (40%) patients had LVSI, and 3/20 (15%) had endocervical invasion. Pelvic washings were positive in 1/16 (7%). Fifteen surgically-staged patients (75%) had Stage I disease (9 IA, 6 IB). Only 1 of the Stage IA patients had LVSI; 1 patient had microcystic, elongated and fragmented (MELF) pattern. None had positive peritoneal cytology. Of the 6 Stage IB patients, 5 (83%) had LVSI. Sixteen patients received adjuvant therapy: 3 (19%) received chemotherapy (CT); 10 (62%), radiation therapy (RT); 2 (12%), CT + RT.

Median time to diagnosis of brain metastases was 29.7 months (range, 6–145 months). Median age at diagnosis of brain metastases was 64.6 years (range, 47.5–86.5 years). Time to diagnosis of brain metastases did not differ between patients with initial Stage I diagnosis and those with advanced disease (p = .92). Brain metastases were the first and isolated site of recurrence in 2/23 (9%) patients. Two patients had spinal cord/extradural disease. Ten (44%) patients were diagnosed with lung metastases at first recurrence (Fig. 1). Of these, 1 had concurrent brain metastases. The median time from diagnosis of lung metastases until diagnosis of brain metastases was 20 months (range, 0–109 months).

Twelve patients had a median time to brain metastases of < 30 months, while 11 had a median time of over 30 months. The two groups did not differ by median age at diagnosis (early presentation, median age 60.2 years (range, 45–76), late presentation, median age 64 years (range, 41–81); p = 1.0), median BMI (early presentation, median BMI 30.0 kg/m^2 (range, 23–43), late presentation, median BMI
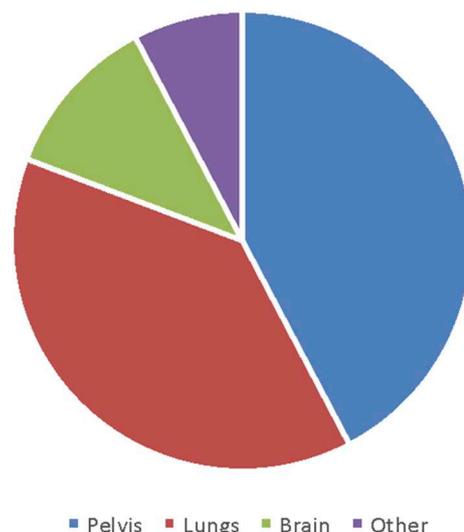

Fig. 1. Anatomic site of first recurrence in women with low-grade endometrioid endometrial adenocarcinoma and brain metastases (n = 23).
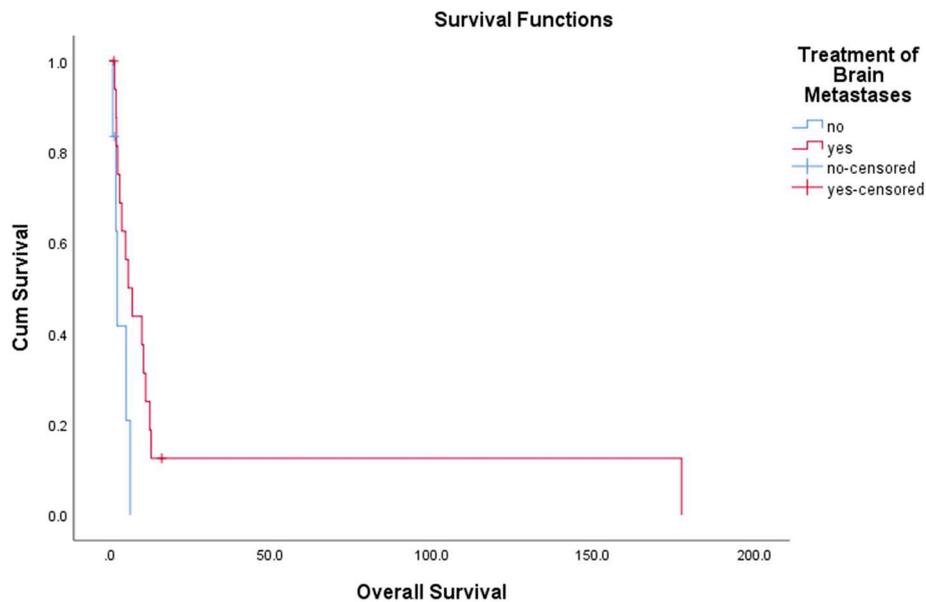
Fig. 2. Overall Survival (OS) for patients with treated and untreated brain metastases ($P = .04$).

29.5 kg/m^2 (range 20–41); $p = .68$), or stage at presentation (early presentation, 6 patients with Stage I, 9 patients with stages II-IV, late presentation, 9 patients with Stage I, 2 patients with Stage II-IV; $p = .19$).

No cases were diagnosed incidentally; all 23 patients presented with neurological complaints, and diagnosis was made based on radiologic findings. Bilateral brain lesions were seen in 12/23 (52%) patients. Solitary brain lesions were seen in 6 (26%) patients. Seventeen of 23 (74%) patients were treated for their brain metastases: 7 received RT; 3, surgery + RT; 1, CT + RT; 4, surgery + CT + RT; 2, surgery + CT; 6 (28%) patients received supportive care only. There was a wide array of chemotherapies used, including paclitaxel, irinotecan, and tamoxifen. Median OS for those who received any treatment was 5.8 months (95% CI, 1.6–10.0 months) versus 3.5 months (95% CI, 1.5–3.3 months; $p = .04$) for those who received best supportive care (Fig. 2). Best supportive care was defined as all modes of treatment that are aimed at helping the patient and caregiver deal with the illness but are not geared towards treating the disease. Median OS for patients with solitary brain lesions was 6.4 months (95% CI, 0–23.7 months) versus 1.3 months for those with multiple brain metastases (95% CI, 2.4–7.5 months; $p = .14$).

4. Discussion

Brain metastases are a rare metastatic complication of EC. The specific incidence and risk factors for the development of brain metastases in patients with low-grade histologies has not been assessed. This study reports on 23 patients who developed brain metastases from low-grade endometrioid EC: 14, grade 2; 9, grade 1. In a previously reported series from Uccella et al., only 4/18 (22%) patients had either grade 1 or 2 histology (Uccella et al., 2016). When Uccella and colleagues combined their results with previously published data, they reported only 9 patients with grades 1–2 disease. Our study of 23 patients represents the largest cohort to date.

The incidence of brain metastases in our study (0.75%) falls within the parameters previously described in the literature for grades 1–3 EC: between 0.3% and 1.2% (Aalders et al., 1984; Henriksen, 1975). In this study and in others, all patients presented with neurological complaints prompting radiographic assessment (Uccella et al., 2016). As such, although EC-related brain lesions are rare, they should be considered in

patients who develop neurological changes. Only 3 of the patients in our study had isolated brain metastases, while the remainder had disease outside the brain as well. Interestingly, several patients also had lung lesions at recurrence, suggesting that their tumors had a propensity for early hematogenous dissemination. The presence of deep myometrial invasion has been suggested as the strongest predictor of hematogenous dissemination, and thus for risk of spread to lung, liver, bone and brain (Mariani et al., 2001). In the current study, however, 5 patients had no myometrial invasion, suggesting that, despite having low-grade, early-stage disease, there may have been some high-risk features inherent to either the tumor or the patient. Fifteen patients had Stage I disease, and the majority of these did not have any additional high-risk factors such as LVSI, MELF pattern, or positive cytology.

Traditionally, ECs have been classified as either type I or type II tumors. Type I tumors are linked to obesity and estrogen excess, and generally have a favorable prognosis. Conversely, type II tumors are primary serous tumors occurring in older, non-obese women, and have a worse outcome. The patients presented in this study all had type I tumors, but had similar outcomes to those seen in type II tumors. Furthermore, the median BMI in our cohort was 29.8 kg/m^2, which is low compared to the BMI reported in traditional studies of type I tumors (Creasman et al., 2017). These data suggest that there may be something inherently different about the behavior of these tumors. Based on TCGA data, some grade 2 and even grade 1 endometrioid tumors fall into the copy-number-high (serous-like) category. Compared to the copy-number-low (endometrioid) category in which the majority of grades 1 and 2 tumors are classified, patients with copy-number-high tumors have the poorest outcomes (Cancer Genome Atlas Research Network et al., 2013). If genomic analyses were performed on the tumors presented in this study, it is plausible that they might have demonstrated features more compatible with the copy-number-high molecular phenotype, potentially supporting the outcomes we observed.

Consistent with other reports, once diagnosed with brain metastases, the patients in our study had a median life expectancy of approximately 5 months (Uccella et al., 2016). However, it is clinically relevant to note that patients who received any treatment for brain metastases had a better median OS compared to those who received best supportive care: 5.8 months (95% CI, 1.6–10.9) versus 2.4 months (95% CI, 1.5–3.3; $p = .04$), respectively.

The current study is limited by its retrospective nature.

Nevertheless, it is the largest series to date of primary brain metastases in low-grade EC. Although rare (comprising approximately 1% of all recurrences in low-grade EC), these tumors are highly lethal. The majority of patients in our study initially presented with Stage I disease, but their brain metastases were not an isolated finding at the time of recurrence. This suggests that some low-grade, early-stage ECs are not low-risk.

In summary, brain metastases are rare events in the progression of low-grade EC, and the development of this complication is heralded by neurological symptoms. In the absence of neurological symptoms, routine brain imaging is not recommended, even in patients with advanced low-grade EC. Treatment of brain lesions is associated with improved survival; however, based on the heterogeneity of treatment in our cohort, we cannot recommend specific therapeutic modalities. Additional studies should clarify the role of radiosurgery and the utility of chemotherapy and radiation therapy in improving outcomes for this patient population.

Author contributions

Paulina Cybulska: Study concept and design; data collection; analysis and interpretation of data and statistics; writing of manuscript; final approval of manuscript.

Marina Stasenko: Data collection; analysis and interpretation of data and statistics; writing of manuscript; final approval of manuscript.

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Jennifer J. Mueller: Critical review of manuscript for important intellectual content; final approval of manuscript.

Mario M. Leitao, Jr.: Analysis and interpretation of data and statistics; writing of manuscript; critical review of manuscript for important intellectual content; final approval of manuscript.

Conflict of Interest Statement

None of the authors declare any conflicts of interest.

Disclosure

Dr. Leitao does ad hoc consulting with Intuitive Surgical, Inc.

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